

Amendment dated February 28, 2005

Reply to Office Action mailed November 28, 2004

Listing of Claims

This listing of claims will replace all prior versions, and listing, of claims in the Application.

1. (CURRENTLY AMENDED) An apparatus for combinatorial chemistry on a substrate comprising:

a substrate having an upper surface, a lower surface, and one or more reaction sites, each reaction site for receiving one or more chemicals;

a first manifold disposed above the substrate and having at least one inlet and one two or more outlets, each outlet positioned to cooperate with one reaction site of the substrate and operable to deliver the one or more chemicals to the one reaction site of the substrate; and

a linear drive for moving the substrate substantially horizontal with respect to below the manifold.

2. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the ~~manifold is defined further as comprising one two or more outlets that form linear delivery spray heads.~~

3. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the ~~manifold delivers one or more chemicals are for nucleic acid synthesis at the one or more reaction sites to the substrate.~~

4. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the ~~manifold delivers one or more chemicals are for peptide synthesis at the one or more reaction sites.~~

5. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the ~~manifold delivers one or more chemicals are for nucleic acid synthesis at the one or more reaction sites.~~

6. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the ~~manifold delivers one or more chemicals are for oligomer synthesis at the one or more reaction sites.~~

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7. (CURRENTLY AMENDED) The apparatus of claim 1, wherein ~~the manifold is further defined as one or more manifolds comprising:~~

~~a the first manifold is operable for delivering an acetonitrile to the substrate manifold; and the apparatus includes~~

~~a second manifold having at least one inlet and two or more outlets operable for delivering an oxidizer to the substrate manifold;~~

~~a third manifold having at least one inlet and two or more outlets operable for delivering a capping reagent to the substrate manifold;~~

~~a fourth manifold having at least one inlet and two or more outlets operable for delivering one or more monomers to the substrate manifold; and~~

~~a fifth manifold having at least one inlet and two or more outlets operable for delivering a deblocking reagent to the substrate manifold.~~

8. (CURRENTLY AMENDED) The apparatus of claim 1, further comprising a mask ~~disposed containing one or more holes positioned~~ between the manifold and the substrate.

9. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the substrate ~~is comprises~~ a chemically nonreactive material.

10. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the substrate ~~is comprises~~ Delrin.

11. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the substrate ~~is comprises~~ Polyethylene.

12. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the substrate ~~is comprises~~ Fiberglass.

13. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the substrate ~~is comprises~~ Glass Micro-fiber filter (GMFF).

14. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the substrate ~~is comprises a material coated with a chemically non-reactive coating.~~

15. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the ~~substrate comprises a top surface and wherein the top upper~~ surface is slanted.

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16. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the one or more reaction sites are the substrate comprises one or more wells.

17. (CANCELLED)

18. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the each of the one or more reaction sites have a substrate comprises a multi-well filter plate.

19. (CURRENTLY AMENDED) The apparatus of claim 16, wherein the one or more wells of the plate have further comprise a slanted interior edge.

20. (CURRENTLY AMENDED) The apparatus of claim 16, wherein the substrate includes plate is further defined as a multi-well filter plate and comprises:

a top portion, and

a bottom plate portion disposed under the top portion, the bottom portion containing the one or more wells; and

a semi-permeable membrane positioned between the top portion and the bottom plate portion.

21. (CURRENTLY AMENDED) The apparatus of claim 16, wherein the one or more wells have comprise a slanted cross-section.

22. (CURRENTLY AMENDED) The apparatus of claim 16, wherein the one or more wells each have comprise a slanted cross-section and a frit.

23. (CURRENTLY AMENDED) The apparatus of claim 16, wherein the one or more wells each have comprise first and second slanted portions.

24. (CURRENTLY AMENDED) The apparatus of claim 22-16, wherein the one or more wells each have comprise a first and second slanted portion, and wherein at least one frit is fixed within the first or second slanted portion of the well.

25. (CURRENTLY AMENDED) The apparatus as in claim 16, wherein each of the one or more wells includes further comprise a synthesis substrate.

26. (CURRENTLY AMENDED) The apparatus of claim 1, further comprising a computer operably connected to and controlling the linear drive.

27. (CURRENTLY AMENDED) The apparatus of claim 1, further comprising one or more chemical reservoirs in fluid communication with the first manifold one or more manifolds.

28. (CURRENTLY AMENDED) The apparatus of claim 28 †, further comprising a computer operably connected to and controlling one or more valves operable for that controlling fluid communication from the flow of fluid between the one or more chemical reservoirs to the first manifold with the one or more manifolds.

29. (CURRENTLY AMENDED) The apparatus of claim 7 †, further comprising: one or more chemical reservoirs in fluid communication with any of the one or more second, third, fourth, and fifth manifolds; and one or more valves operable for controlling the flow of fluid communication from the one or more chemical reservoirs to any of the one or more second, third, fourth, and fifth manifolds.

30. (CURRENTLY AMENDED) The apparatus of claim 1, further comprising a mask positioned on the upper surface of between the manifold and the substrate.

31. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask positioned between the manifold and the substrate is layered on the upper surface of the substrate.

32. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the a mask is positioned further comprises has one or more through-holes, each through-hole disposed generally over at least one or more reaction sites of the substrate.

33. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises Teflon™.

34. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises Teflon™ between 0.002 and 0.25 inches thick.

35. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises polyethylene.

36. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises fiberglass.

37. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises Delrin.

38. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises polypropylene.

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39. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises single-sided Teflon™ tape.

40. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises molded polypropylene having and further comprising one or more divots that generally match the one or more reaction sites wells of the a substrate.

41. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask has dynamically adjustable openings comprises molded polyethylene and further comprising divots that generally match one or more wells of a substrate.

42. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises a magnetically attractive material.

43. (CURRENTLY AMENDED) The apparatus of claim 30, wherein the mask is comprises an electrostatic charge opposite an electrostatic charge on the substrate.

44. (CURRENTLY AMENDED) The apparatus of claim 1, further comprising a vacuum in operable communication with the substrate.

45. (CURRENTLY AMENDED) The apparatus as in claim 1, wherein the one or more reaction sites substrate comprises have one or more reactive groups protected from a chemical reaction by one or more removable protecting groups.

46. (ORIGINAL) The apparatus of claim 45, wherein the one or more removable protecting groups is removed by addition of a deblocking reagent.

47. (CURRENTLY AMENDED) The apparatus of claim 45, wherein at the one or more reaction sites substrate comprises is one or more monomers for nucleic acid synthesis.

48. (CURRENTLY AMENDED) The apparatus of claim 45, wherein at the one or more reaction sites substrate comprises is one or more monomers for peptide synthesis.

49. (CURRENTLY AMENDED) The apparatus of claim 45, wherein at the one or more reaction sites substrate comprises is one or more monomers for peptide nucleic acid synthesis.

50. (CURRENTLY AMENDED) The apparatus of claim 45, wherein at the one or more reaction sites substrate comprises is one or more monomers for carbohydrate synthesis.

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51. (CURRENTLY AMENDED) The apparatus of claim 45, wherein at the one or more reaction sites substrate further comprises is a linker.

52. (CURRENTLY AMENDED) The apparatus of claim 45, wherein at the one or more reaction sites substrate comprises is a small molecule library.

53. (CURRENTLY AMENDED) The apparatus of claim 1, wherein the one or more reaction sites substrate comprises are on the order of 6, 12, 48, 96, 384, 864, 1,536 or more reaction sites.

54. (ORIGINAL) The apparatus of claim 1, wherein the substrate is rectangular.

55. (CURRENTLY AMENDED) The apparatus as in claim 1, wherein the one or more reaction sites each consist of a well that is canted substrate comprises one or more wells, and the one or more wells are canted.

56. (CURRENTLY AMENDED) An apparatus for combinatorial chemistry comprising:

a substrate for receiving one or more chemicals, the substrate having an upper surface, a lower surface and comprising one or more reaction sites;

a mask positioned on the upper surface of the substrate;

a one or more manifolds positioned above the mask for cooperation with at least a portion of the substrate, each manifold having at least one inlet and two or more outlets, each outlet operable to deliver the one or more chemicals to at least one reaction site at least a portion of the substrate; and

a linear drive disposed under the substrate for moving the substrate substantially horizontal with respect to the manifold and the mask below for providing cooperation between the substrate and at least a portion of the one or more linear manifolds.

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57. (CURRENTLY AMENDED) An apparatus for combinatorial chemistry comprising:

a substrate for receiving one or more chemicals, the substrate having an upper surface, a lower surface, vacuum lines and comprising one or more reaction sites;

a mask comprising having one or more through holes, the mask positioned generally over the one or more reaction sites generally on the upper surface of the substrate;

a one or more linear manifolds positioned above the mask, for cooperation with at least a portion of the substrate, each linear manifold having at least one inlet and two or more outlets, each outlet operable to deliver the one or more chemicals to at least one reaction site of the substrate;

a linear drive disposed under the substrate for moving the substrate substantially horizontal with respect to the manifold and the mask below for providing cooperation between the substrate and at least a portion of the one or more linear manifolds; and

a vacuum disposed below the ~~one or more reaction sites~~ lower surface of the substrate.

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58. (CURRENTLY AMENDED) An apparatus for synthesizing oligomers comprising:

a substrate for receiving one or more chemicals, the substrate having an upper surface, a lower surface, vacuum lines and comprising one or more reaction sites;

a mask comprising having one or more through holes, the mask positioned generally over the one or more reaction sites generally on the upper surface of the substrate;

one or more linear manifolds positioned above the mask, for cooperation with at least a portion of the substrate, each manifold having at least one inlet and two or more outlets, each outlet operable to deliver the one or more chemicals to at least one reaction site of the substrate, the one or more linear manifolds further comprising:

a first manifold having at least one inlet and two or more outlets operable for delivering an acetonitrile to the substrate manifold;

a second manifold having at least one inlet and two or more outlets operable for delivering an oxidizer to the substrate manifold;

a third manifold having at least one inlet and two or more outlets operable for delivering a capping reagent to the substrate manifold;

a fourth manifold having at least one inlet and two or more outlets operable for delivering one or more monomers to the substrate manifold; and

a fifth manifold having at least one inlet and two or more outlets operable for delivering a deblocking reagent to the substrate manifold;

a linear motion table disposed under the substrate for moving that moves the substrate substantially horizontal with respect to the manifold and for providing cooperation between the substrate and at least a portion of the one or more linear the mask below the one or more manifolds; and

a vacuum disposed below the one or more reaction sites lower surface of the substrate.

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59. (WITHDRAWN) A method for controlling a chemical reaction in one or more reaction sites protected by a mask comprising the steps of:

positioning a mask comprising one or more wells over a substrate comprising one or more reaction sites;

flooding a deblock reagent over the surface of the mask, wherein the deblock reagent will only enter unmasked reaction sites;

removing the mask;

flooding a mix of activator and one reactive monomer into all reaction sites;

flooding a mix of cap A and B reagents into all reaction sites;

flooding and oxidizing reagent into all reaction sites; and

repeating the above steps for the other reactive monomers.

60. (WITHDRAWN) A method for controlling a chemical reaction in one or more reaction sites protected by a mask comprising the steps of:

(a) flooding a deblock reagent into all the reaction sites of a substrate;

(b) positioning a monomer-specific mask for a specific monomer over a substrate;

(c) flood a specific monomer and activator over the substrate, wherein only those reaction sites with open holes in the mask will receive one or more specific monomers;

(d) removing the mask; and

(e) repeating steps (b) through (d) for each specific monomer;

(f) flooding a mix of cap A and B reagents into all reaction sites; and

(g) flooding an oxidizing reagent into all reaction sites.

61. (CURRENTLY AMENDED) A mask for chemical synthesis comprising:

a non-reactive sheet having a top surface, and a bottom surface, ; one or more through-holes that form an array, and one or more outlets disposed below the one or more through-holes, wherein the one or more through-holes are defined and positioned to work in cooperation with defined portions of a substrate, the defined portions of the substrate that generally match the position of being one or more wells of a the substrate.

62. (CANCELLED)

63. (CANCELLED)

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64. (CURRENTLY AMENDED) The mask of claim 61, wherein the mask non-reactive sheet is comprises a substantially chemically non-reactive material.

65. (CURRENTLY AMENDED) The mask of claim 61, wherein the mask non-reactive sheet is comprises a Teflon™-coated polymer.

66. (CURRENTLY AMENDED) The mask of claim 61, wherein the mask non-reactive sheet is comprises polyethylene.

67. (CURRENTLY AMENDED) The mask of claim 61, wherein the mask non-reactive sheet is comprises fiberglass.

68. (CURRENTLY AMENDED) The mask of claim 61, wherein the mask non-reactive sheet is comprises Delrin.

69. (CURRENTLY AMENDED) The mask of claim 61, wherein the mask non-reactive sheet is comprises polypropylene.

70. (CANCELLED)

71. (CURRENTLY AMENDED) The mask of claim 61 70, ~~wherein the through-holes are further defined as having one or more nozzles on the bottom surface, wherein the one or more outlets nozzles have an angle that matches the an angle of the one or more wells in the multi-well plate.~~

72. (CURRENTLY AMENDED) The mask of claim 61 70, ~~wherein the through-holes are further defined as having one or more nozzles on the bottom surface, wherein the one or more outlets nozzles have an angle that is more than the an angle of the one or more wells in the multi-well plate.~~

73. (CURRENTLY AMENDED) The mask of claim 61 70, ~~wherein the through-holes are further defined as having one or more nozzles on the bottom surface, wherein the one or more outlets nozzles have an angle that is less than the an angle of the one or more wells in the multi-well plate.~~

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74. (WITHDRAWN) A method of determining synthetic order of monomer addition comprising the steps of:

- determining the synthesis order for the addition of a specific monomer;
- deciding whether a mask is to be positioned on a substrate;
- moving the substrate to a preselected position for chemical addition;
- adding a specific monomer;
- washing the substrate; and
- repeating the above steps if another monomer is to be added.

75. (WITHDRAWN) The method of claim 74, wherein the step of catalyzing the addition of a monomer is defined further as comprising the steps of:

- performing a deblock step;
- putting on a mask to protect sites in which a monomer will not be added;
- delivering one or more monomers;
- performing a capping steps and performing an oxidizer step.

76. (WITHDRAWN) A method for producing polymers comprising the steps of:
placing a reactive compound on one or more reaction sites of a substrate;
protecting one or more reaction sites of a substrate with a mask; and
controlling a chemical reaction in the one or more reaction sites not protected by the mask.

77. (WITHDRAWN) The method of claim 76, wherein the step of controlling a reaction is defined further as not deblocking the reactive compound.

78. (WITHDRAWN) The method of claim 76, wherein the step of controlling a chemical reaction comprises the steps of:

- flooding a deblocking reagent over the surface of the mask;
- flooding a coupling reagent over the surface of the mask, wherein the coupling reagent comprises one or more reactive compounds;
- flooding a capping reagent over the surface of the mask; and
- flooding oxidizing reagent over the surface of the mask.

79. (WITHDRAWN) The method of claim 76, wherein the one or more reactive compounds are defined further as phosphoramidite comprising compounds.

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80. (WITHDRAWN) The method of claim 76, wherein phosphoramidite comprising compounds include one or more protected phosphoramidite nucleic acid bases A, G, C, T, U or derivatives thereof.

81. (WITHDRAWN) The method of claim 76, wherein chemical reaction is the addition of one or more monomers for carbohydrate synthesis.

82. (WITHDRAWN) The method of claim 76, wherein chemical reaction is the addition of one or more monomers for nucleic acid synthesis.

83. (WITHDRAWN) The method of claim 76, wherein chemical reaction is the addition of one or more monomers for peptide synthesis.

84. (WITHDRAWN) The method of claim 76, wherein the capping agent further comprises a cap A and a cap B reagent and wherein they acetylate unreacted termini.

85. (WITHDRAWN) A method of determining the mask pattern for monomer addition comprising the steps of:

reading the sequence of one or more monomer sequences;

setting up an array that contains all the possible permutations of the monomers wherein each of these permutations having a first and a second element, wherein the first element records the number of cycles required to complete synthesis and the second element records the number of monomers to be deblocked;

selecting a variable number that equals the total number of required monomers types;

selecting a second variable that contains the total number of wells; and

testing the array for the minimum number of masks that are required to complete all the monomer additions; and

selecting the array that contains the minimum number of masks.

86. (WITHDRAWN) The method of claim 85, further comprising the step of pre-determining areas with sequences in common within the sequences of the one or more monomers and preparing masks for those areas of with sequences in common independent from the determination of the array.